

=> file reg

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STRUCTURE FILE UPDATES: 31 MAR 2003 HIGHEST RN 501072-24-8  
DICTIONARY FILE UPDATES: 31 MAR 2003 HIGHEST RN 501072-24-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when  
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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP  
PROPERTIES for more information. See STNote 27, Searching Properties  
in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> d 15

L5 ANSWER-1-OF 1 REGISTRY COPYRIGHT 2003 ACS

RN 314266-76-7 REGISTRY

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginy- (2R,4S,5S)-5-  
amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
(CA INDEX NAME)

OTHER NAMES:

CN OM 99-2

FS PROTEIN SEQUENCE; STEREOSEARCH

DR 313355-78-1

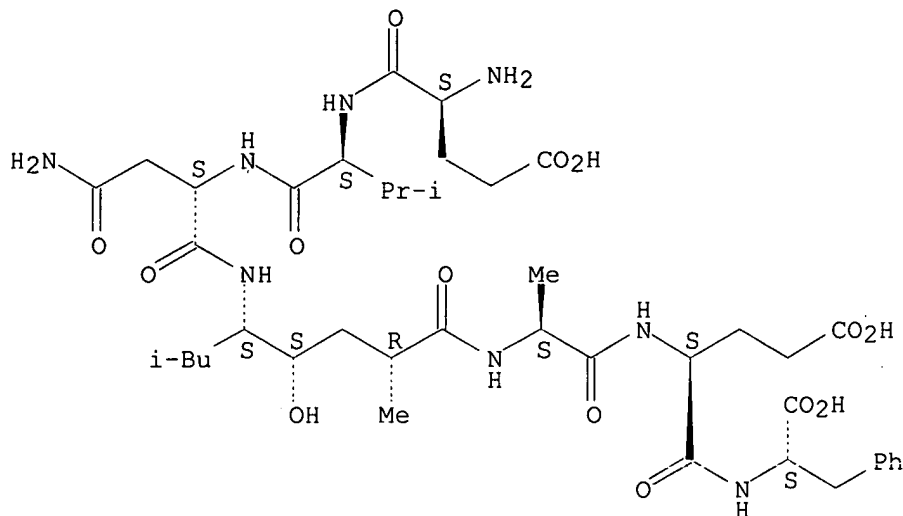
MF C41 H64 N8 O14

SR CA

LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, TOXCENTER, USPATFULL

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

Absolute stereochemistry.



9 REFERENCES IN FILE CA (1962 TO DATE)  
 3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 9 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> file caplus

FILE 'CAPLUS' ENTERED AT 14:25:11 ON 01 APR 2003  
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FILE COVERS 1907 - 1 Apr 2003 VOL 138 ISS 14  
 FILE LAST UPDATED: 31 Mar 2003 (20030331/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file caplus; d que 18

FILE 'CAPLUS' ENTERED AT 14:32:53 ON 01 APR 2003  
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FILE COVERS 1907 - 1 Apr 2003 VOL 138 ISS 14  
FILE LAST UPDATED: 31 Mar 2003 (20030331/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L5 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C41H64N8O14/MF

L6 8 SEA FILE=CAPLUS ABB=ON PLU=ON L5

L7 118341 SEA FILE=CAPLUS ABB=ON PLU=ON ?ALZHEIMER? OR ?DEMENTIA? OR ?MEMOR?

6 SEA FILE=CAPLUS ABB=ON PLU=ON L6 AND L7

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FILE 'USPATFULL' ENTERED AT 14:33:15 ON 01 APR 2003  
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 1 Apr 2003 (20030401/PD)  
FILE LAST UPDATED: 1 Apr 2003 (20030401/ED)  
HIGHEST GRANTED PATENT NUMBER: US6543053  
HIGHEST APPLICATION PUBLICATION NUMBER: US2003061649  
CA INDEXING IS CURRENT THROUGH 1 Apr 2003 (20030401/UPCA)  
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 1 Apr 2003 (20030401/PD)  
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2003  
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2003

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>>> USPAT2 is now available.  USPATFULL contains full text of the  <<<
>>> original, i.e., the earliest published granted patents or  <<<
>>> applications.  USPAT2 contains full text of the latest US  <<<
>>> publications, starting in 2001, for the inventions covered in  <<<
>>> USPATFULL.  A USPATFULL record contains not only the original  <<<
>>> published document but also a list of any subsequent  <<<
>>> publications.  The publication number, patent kind code, and  <<<
>>> publication date for all the US publications for an invention  <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL  <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc.  <<<
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>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<
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This file contains CAS Registry Numbers for easy and accurate substance identification.

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        BI).
L5      1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND C41H64N8O14/MF
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L10     496190 SEA FILE=USPATFULL ABB=ON  PLU=ON  ?ALZHEIMER? OR ?DEMENTIA?
        OR ?MEMOR?
L11     3 SEA FILE=USPATFULL ABB=ON  PLU=ON  L9 AND L10
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FILE 'CAPLUS' ENTERED AT 14:33:24 ON 01 APR 2003  
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 PROCESSING COMPLETED FOR L11

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L13     9 DUP-REM L8 L11 (0 DUPLICATES REMOVED)
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        ANSWERS '7-9' FROM FILE USPATFULL
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L13 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:153949 CAPLUS
DOCUMENT NUMBER: 136:305914
TITLE: Substrate and inhibitor profile of BACE
        (.beta.-secretase) and comparison with other mammalian
        aspartic proteases
AUTHOR(S): Gruninger-Leitch, Fiona; Schlatter, Daniel; Kung,
        Erich; Nelbock, Peter; Dobeli, Heinz
CORPORATE SOURCE: CNS Research, Hoffmann-La Roche Ltd, Basel, CH-4070,
        Switz.
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SOURCE: Journal of Biological Chemistry (2002), 277(7), 4687-4693  
 CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

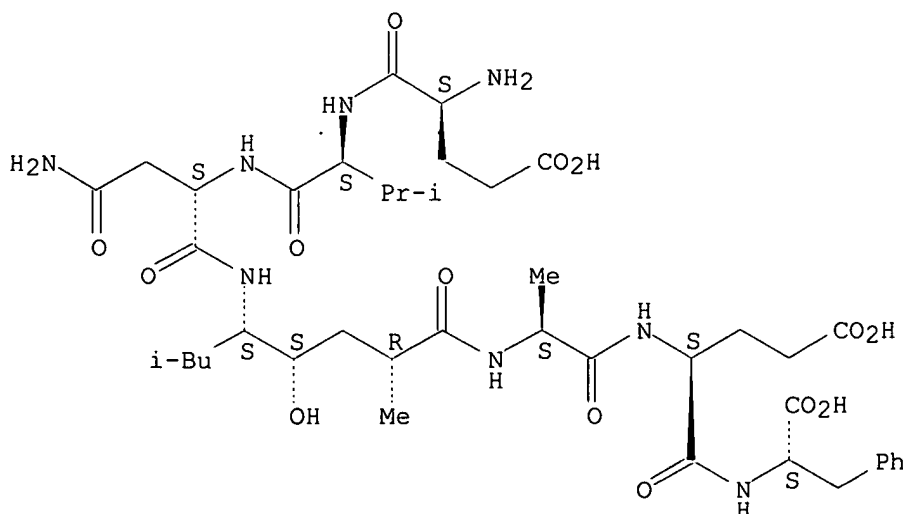
AB The full-length and ectodomain forms of .beta.-site APP cleavage enzyme (BACE) have been cloned, expressed in Sf9 cells, and purified to homogeneity. This aspartic protease cleaves the amyloid precursor protein at the .beta.-secretase site, a crit. step in the **Alzheimer's** disease pathogenesis. Comparison of BACE to other aspartic proteases such as cathepsin D and E, napsin A, pepsin, and renin revealed little similarity with respect to the substrate preference and inhibitor profile. On the other hand, these parameters are all very similar for the homologous enzyme BACE2. Based on a collection of decameric substrates, it was found that BACE has a loose substrate specificity and that the substrate recognition site in BACE extends over several amino acids. In common with the aspartic proteases mentioned above, BACE prefers a leucine residue at position P1. Unlike cathepsin D etc., BACE accepts polar or acidic residues at positions P2' and P1 but prefers bulky hydrophobic residues at position P3. BACE displays poor kinetic consts. toward its known substrates (wild-type substrate, SEVKM .dwnarw. DAEFR,  $K_m = 7 \text{ .}\mu\text{M}$ ,  $K_{cat} = 0.002 \text{ s}^{-1}$ ; Swedish mutant, SEVNL .dwnarw. DAEFR,  $K_m = 9 \text{ .}\mu\text{M}$ ,  $K_{cat} = 0.02 \text{ s}^{-1}$ ). A new substrate (VVEVDA .dwnarw. AVTP,  $K_m = 1 \text{ .}\mu\text{M}$ ,  $K_{cat} = 0.004$ ) was identified by serendipity.

IT 314266-76-7, OM99-2  
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (substrate and inhibitor profile of BACE .beta.-secretase and comparison with other mammalian aspartic proteases)

RN 314266-76-7 CAPLUS

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:728546 CAPLUS  
DOCUMENT NUMBER: 138:85411  
TITLE: Recombinant insect cell expression and purification of human .beta.-secretase (BACE-1) for X-ray crystallography  
AUTHOR(S): Bruinzeel, Wouter; Yon, Jeff; Giovannelli, Silvio; Masure, Stefan  
CORPORATE SOURCE: Department of Assay Development & HTS, Johnson & Johnson Pharmaceutical Research & Development, Beerse, B-2340, Belg.  
SOURCE: Protein Expression and Purification (2002), 26(1), 139-148  
CODEN: PEXPEJ; ISSN: 1046-5928  
PUBLISHER: Elsevier Science  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Human .beta.-secretase (BACE-1) is a type I integral membrane aspartic protease that catalyzes the internal cleavage of the amyloid precursor protein (APP), generating the N-terminus of the A.beta. peptide. The generation and subsequent extracellular deposition of A.beta.1-42 peptide into amyloid plaques in the brain constitute one of the hallmarks of **Alzheimer's** disease (AD), a common debilitating neurodegenerative disorder. Inhibition of BACE-1 is considered an excellent therapeutic strategy against AD. To generate pure enzyme for protein crystallog. and subsequent structure-based drug design, we have expressed a sol., unglycosylated, 6.times.His-tagged form of proBACE-1 in insect cells using baculovirus infection. To avoid prodn. of a mixt. of the pro-enzyme form and the mature form of BACE-1, the proprotein convertase furin was coexpressed with proBACE-1, leading to almost complete proteolytic activation of the recombinant enzyme. The mature enzyme was secreted in the conditioned medium of BACE-1/furin coinfectd HighFive insect cells. Secreted BACE-1 protein was purified to homogeneity from the medium using subsequent Ni-chelate affinity chromatog., anion-exchange chromatog., hydrophobic interaction chromatog., and gel filtration. To avoid autoproteolysis, all purifn. steps were performed at pH values outside the activity range of BACE-1. The purified, biol. active enzyme was homogeneous on SDS/PAGE and had the expected sequence and mol. mass detd. by N-terminal amino acid sequencing and mass spectrometry, resp. Moreover, the prepn. showed a single peak of the expected size with only 17% polydispersity using dynamic light scattering anal. The yield of BACE-1 from fermn. cultures was approx. 0.1 mg pure enzyme per L of cell culture medium. The purified protein was successfully used to generate BACE-1/inhibitor co-crystals and to det. the crystal structure of the complex by X-ray anal. The availability of substantial quantities of active, homogeneous enzyme will be of great help in future structure-based drug design efforts in the search for efficient protease inhibitor drugs to treat AD.

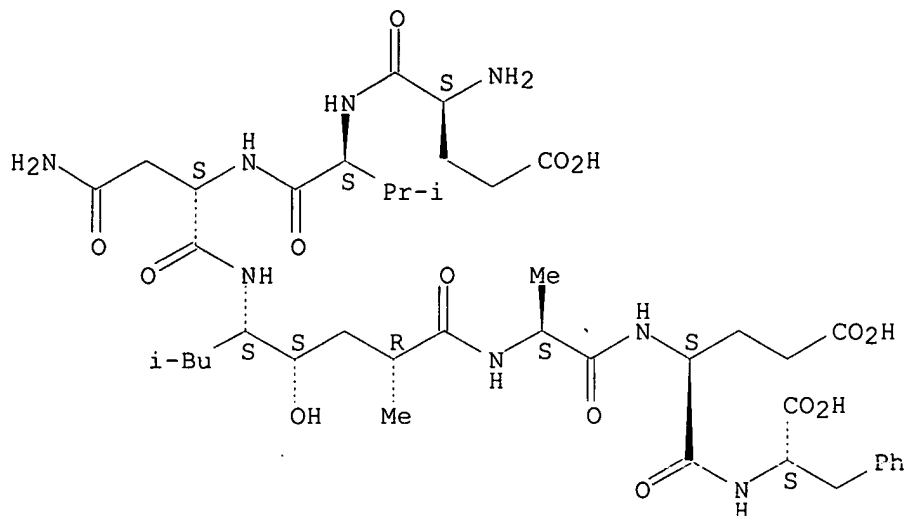
IT 314266-76-7, OM 99-2

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(recombinant insect cell expression and purifn. of human .beta.-secretase (BACE-1))

RN 314266-76-7 CAPLUS

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:12489 CAPLUS

DOCUMENT NUMBER: 134:80832

TITLE: Inhibitors of memapsin 2 and use thereof

INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois

SOURCE: PCT Int. Appl., 86 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE       |
|------------------------|--|----------|-----------------|------------|
| WO 2001000665          | A2   | 20010104 | WO 2000-US17742 | 20000627   |
| WO 2001000665          | A3   | 20010927 |                 |            |
| WO 2001000665          | C2   | 20020725 |                 |            |
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| RW:                    | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG   |          |                 |            |
| EP 1194449             | A2   | 20020410 | EP 2000-943236  | 20000627   |
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| JP 2003506322          | T2   | 20030218 | JP 2001-507071  | 20000627   |
| US 2002049303          | A1   | 20020425 | US 2001-796264  | 20010228   |
| US 2002164760          | A1   | 20021107 | US 2001-795903  | 20010228   |
| US 2002115600          | A1   | 20020822 | US 2001-845226  | 20010430   |
| PRIORITY APPLN. INFO.: |  |          | US 1999-141363P | P 19990628 |

US 1999-168060P P 19991130  
 US 2000-177836P P 20000125  
 US 2000-178368P P 20000127  
 US 2000-210292P P 20000608  
 US 2000-603713 A3 20000627 ✓  
 US 2000-604608 A3 20000627  
 WO 2000-US17742 W 20000627

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is  $1.6 \times 10^{-9}$  M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

IT 314266-76-7P, OM 99-2

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

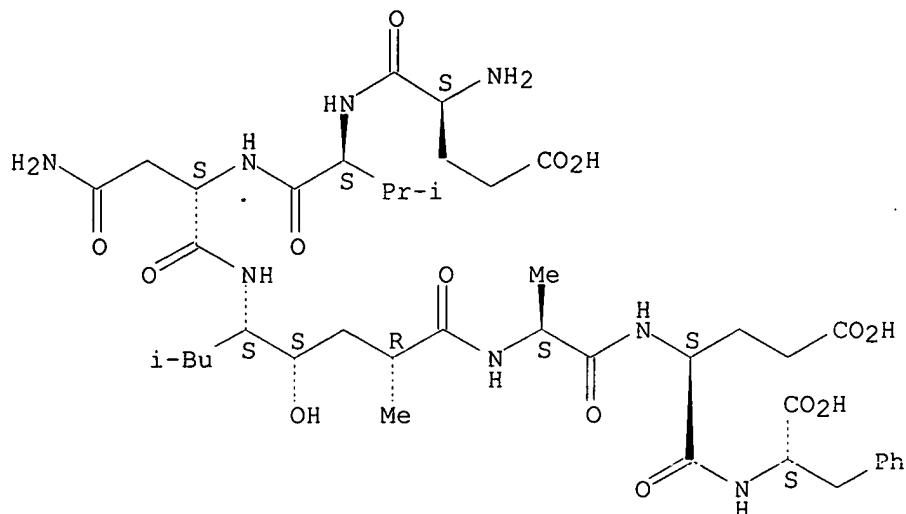
(inhibitors of memapsin 2 and use thereof)

RN 314266-76-7 CAPLUS

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyL-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry.





IT 314266-76-7

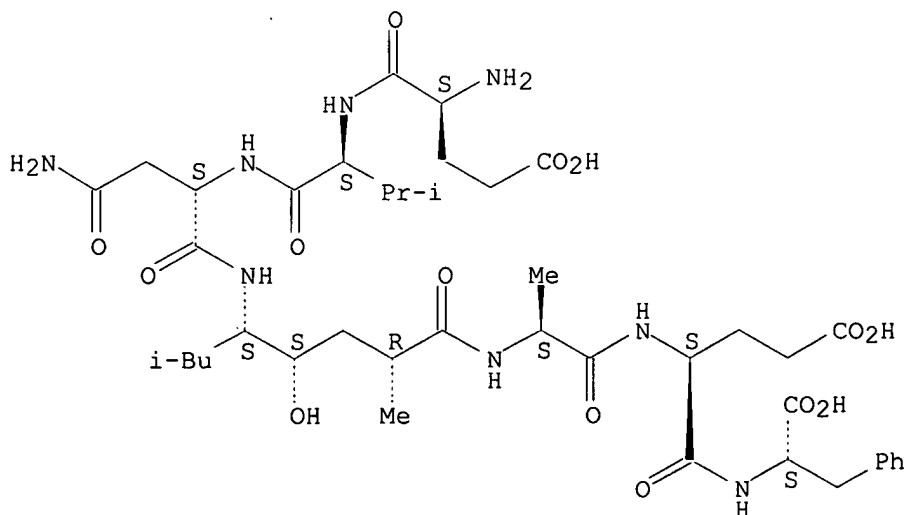
RL: PRP (Properties)

(unclaimed sequence; inhibitors of memapsin 2 and use thereof)

RN 314266-76-7 CAPLUS

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:12487 CAPLUS

DOCUMENT NUMBER: 134:68049

TITLE: Catalytically active recombinant memapsin 2, 3D  
crystal structure based inhibitor design, synthesis,  
and screening, for Alzheimer's disease  
treatment

INVENTOR(S): Tang, Jordan J. N.; Lin, Xinli; Koelsch, Gerald  
 PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA  
 SOURCE: PCT Int. Appl., 87 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE          |
|---|------|----------|-----------------|---------------|
| WO 2001000663   | A2   | 20010104 | WO 2000-US17661 | 20000627      |
| WO 2001000663   | A3   | 20011004 |                 |               |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  |      |          |                 |               |
| EP 1196609  | A2   | 20020417 | EP 2000-943208  | 20000627      |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO   |      |          |                 |               |
| JP 2003503072   | T2   | 20030128 | JP 2001-507069  | 20000627      |
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|   |      |          | US 2000-604608  | A3 20000627   |
|   |      |          | WO 2000-US17661 | W 20000627    |
| AB A method for producing catalytically active recombinant memapsin 2 comprising expression in a bacteria and refolding the recombinant memapsin 2 under conditions which dissoc. and then slowly refold the enzyme into a catalytically active form is disclosed. A method of isolating inhibitors of cleavage by memapsin 2 comprising adding to one or more potential inhibitors of catalytically active recombinant memapsin 2, and a substrate for memapsin 2, and screening for decreased cleavage of the substrate by the inhibitors, wherein the inhibitors are in a library of small synthetic mols., like proteins and peptides. Alternatively, the inhibitors are oligonucleotides preventing or decreasing expression of catalytically active memapsin 2. A method for designing or obtaining inhibitors of catalytically active memapsin 2 comprising modeling an inhibitor based on the crystn. coordinates of memapsin 2 or parameters. A database comprising binding properties and chem. structures of compds. designed or screened by modeling an inhibitor based on the crystn. coordinates of memapsin 2 or parameters is claimed. A method of treating or preventing Alzheimer's disease comprising administering to a patient in need thereof an inhibitor of memapsin 2 which binds to the active site of the memapsin 2 defined by the presence of two catalytic aspartic residues and substrate binding cleft, is also claimed. The cDNAs of two new human membrane-assocd. aspartic proteases, memapsin 1 and memapsin 2, have been cloned and sequenced. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate |      |          |                 |               |

analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Fig. 1). The inhibition const. of OM99-2 is  $1.6 \times 10^9$  M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of **Alzheimer's** disease.

IT 314266-76-7DP, OM 99-2, complexes with memapsin 2

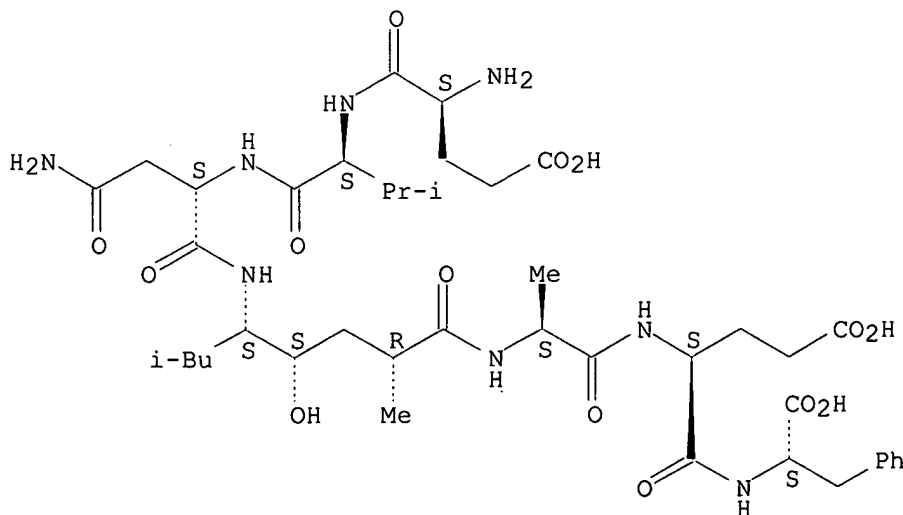
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(catalytically active recombinant memapsin 2, 3D crystal structure based inhibitor design, synthesis, and screening, for **Alzheimer's** disease treatment)

RN 314266-76-7 CAPLUS

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry. .



L13 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:558376 CAPLUS

DOCUMENT NUMBER: 135:282682

TITLE: Structure-based design: potent inhibitors of human brain memapsin 2 (.beta.-secretase)

AUTHOR(S): Ghosh, Arun K.; Bilcer, Geoffrey; Harwood, Cynthia; Kawahama, Reiko; Shin, Dongwoo; Hussain, Khaja Azhar;

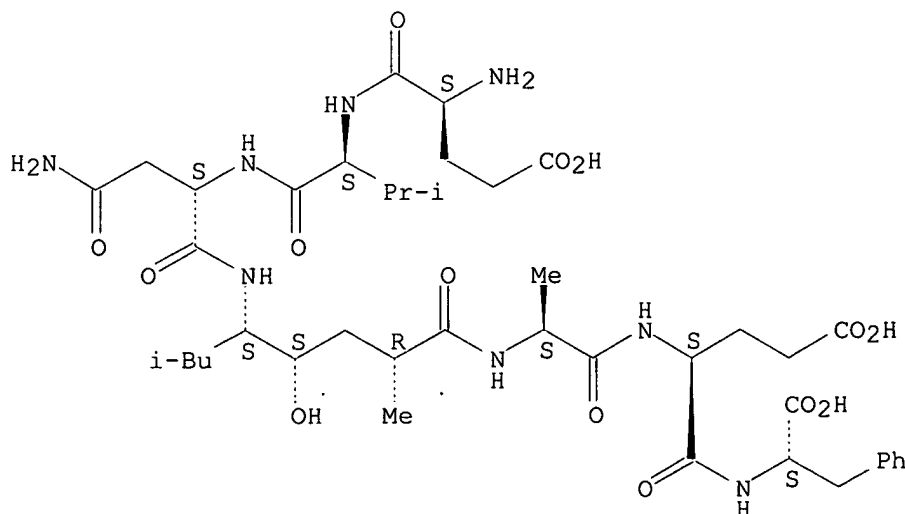
Hong, Lin; Loy, Jeffrey A.; Nguyen, Chan; Koelsch, Gerald; Ermoloeff, Jacques; Tang, Jordan  
 CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, 60607, USA  
 SOURCE: Journal of Medicinal Chemistry (2001), 44(18), 2865-2868  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Memapsin 2 (.beta.-secretase) is one of two proteases that cleave the .beta.-amyloid precursor protein (APP) to produce the 40-42 residue amyloid-.beta. peptide (A.beta.) in the human brain, a key event in the progression of **Alzheimer's** disease. On the basis of the X-ray crystal structure of our lead inhibitor (2, OM99-2 with eight residues) bound to memapsin, we have reduced the mol. wt. and designed potent memapsin inhibitors. Structure-based design and preliminary structure-activity studies have been presented.

IT 314266-76-7, OM 99-2  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (structure-based design of memapsin 2 inhibitors for the treatment of **Alzheimer's** disease)

RN 314266-76-7 CAPLUS  
 CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:724245 CAPLUS

DOCUMENT NUMBER: 134:53089

TITLE: Structure of the protease domain of memapsin 2 (.beta.-secretase) complexed with inhibitor

AUTHOR(S): Hong, Lin; Koelsch, Gerald; Lin, Xinli; Wu, Shili;

Terzyan, Simon; Ghosh, Arun K.; Zhang, Xuenjun C.;  
 Tang, Jordan  
 CORPORATE SOURCE: Protein Studies Program, Oklahoma Medical Research  
 Foundation, Oklahoma City, OK, 73104, USA  
 SOURCE: Science (Washington, D. C.) (2000), 290(5489), 150-153  
 CODEN: SCIEAS; ISSN: 0036-8075  
 PUBLISHER: American Association for the Advancement of Science  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Memapsin 2 (.beta.-secretase) is a membrane-assocd. aspartic protease  
 involved in the prodn. of .beta.-amyloid peptide in **Alzheimer's**  
 disease and is a major target for drug design. We detd. the crystal  
 structure of the protease domain of human memapsin 2 complexed to an  
 eight-residue inhibitor at 1.9 angstrom resoln. The active site of  
 memapsin 2 is more open and less hydrophobic than that of other human  
 aspartic proteases. The subsite locations from S4 to S2' are well  
 defined. A kink of the inhibitor chain at P2' and the change of chain  
 direction of P3' and P4' may be mimicked to provide inhibitor selectivity.

IT 314266-76-7D, OM 99-2, complexes with memapsin 2

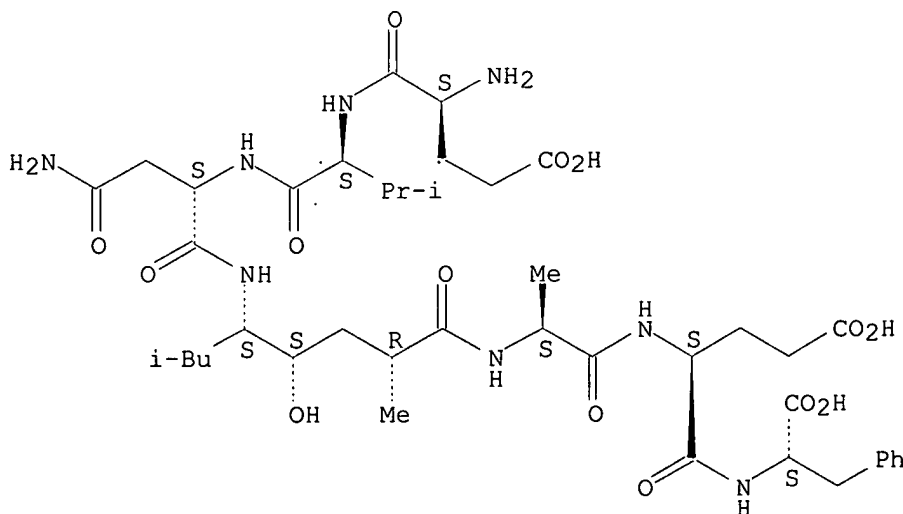
RL: PRP (Properties)

(structure of the protease domain of memapsin 2 (.beta.-secretase)  
 complexed with inhibitor)

RN 314266-76-7 CAPLUS

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-  
 amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 9 USPATFULL

ACCESSION NUMBER: 2002:294717 USPATFULL

TITLE: Catalytically active recombinant memapsin and methods  
 of use thereof

INVENTOR(S): Lin, Xinli, Edmond, OK, UNITED STATES

Koelsch, Gerald, Oklahoma City, OK, UNITED STATES

Tang, Jordan J.N., Edmond, OK, UNITED STATES

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation

|                       | NUMBER   | KIND | DATE         |
|-----------------------|--|------|--------------|
| PATENT INFORMATION:   | US 2002164760  | A1   | 20021107     |
| APPLICATION INFO.:    | US 2001-795903   | A1   | 20010228 (9) |
| RELATED APPLN. INFO.: | Division of Ser. No. US 2000-604608, filed on 27 Jun 2000, PENDING |      |              |

|                       | NUMBER  | DATE          |
|-----------------------|---|---------------|
| PRIORITY INFORMATION: | US 1999-141363P   | 19990628 (60) |
|                       | US 1999-168060P   | 19991130 (60) |
|                       | US 2000-177836P   | 20000125 (60) |
|                       | US 2000-178368P   | 20000127 (60) |
|                       | US 2000-210292P   | 20000608 (60) |
| DOCUMENT TYPE:        | Utility   |               |
| FILE SEGMENT:         | APPLICATION   |               |
| LEGAL REPRESENTATIVE: | PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400 |               |
| NUMBER OF CLAIMS:     | 33  |               |
| EXEMPLARY CLAIM:      | 1   |               |
| NUMBER OF DRAWINGS:   | 12 Drawing Page(s)  |               |
| LINE COUNT:           | 2440  |               |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for the production of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been determined. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogues including isosteres at the sites of the critical amino acid residues were developed and the substrate analogues, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (FIG. 1). The inhibition constant of OM99-2 is 1.6.times.10.sup.-9 M against recombinant pro-memapsin 2. Crystallography of memapsin 2 bound to this inhibitor was used to determine the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using commercially available software programs and techniques familiar to those in organic chemistry and enzymology, to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of **Alzheimer's** disease.

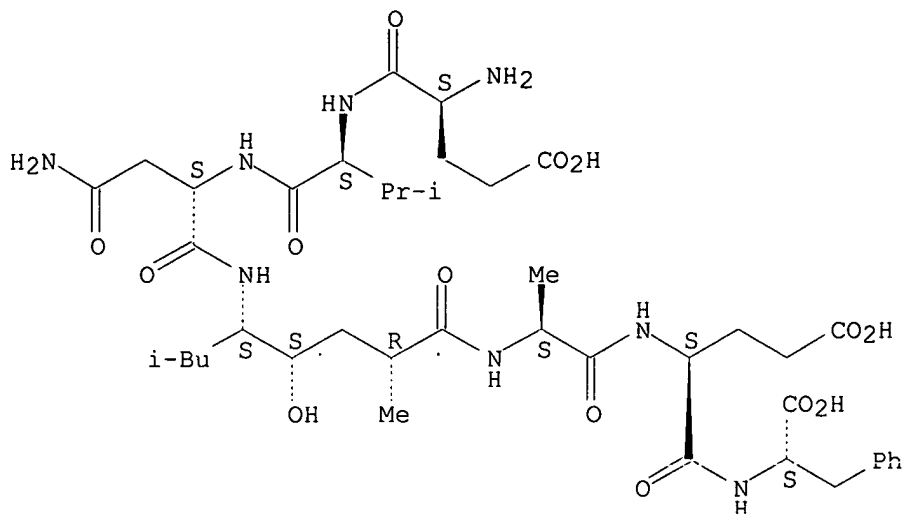
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **314266-76-7DP**, OM 99-2, complexes with memapsin 2  
 (catalytically active recombinant memapsin 2, 3D crystal structure based inhibitor design, synthesis, and screening, for Alzheimer's disease treatment)

RN 314266-76-7 USPATFULL

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyL-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
 (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 8 OF 9 USPATFULL

ACCESSION NUMBER: 2002:214213 USPATFULL  
 TITLE: Inhibitors of memapsin 2 and use thereof  
 INVENTOR(S): Koelsch, Gerald, Oklahoma City, OK, UNITED STATES  
 Tang, Jordan J.N., Edmond, OK, UNITED STATES  
 Hong, Lin, Oklahoma City, OK, UNITED STATES  
 Ghosh, Arun K., River Forest, IL, UNITED STATES  
 PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation (U.S. corporation)

|                       | NUMBER   | KIND | DATE         |
|-----------------------|--|------|--------------|
| PATENT INFORMATION:   | US 2002115600  | A1   | 20020822     |
| APPLICATION INFO.:    | US 2001-845226   | A1   | 20010430 (9) |
| RELATED APPLN. INFO.: | Division of Ser. No. US 2000-603713, filed on 27 Jun 2000, PENDING |      |              |

|                       | NUMBER   | DATE          |
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|                       | US 1999-168060P  | 19991130 (60) |
|                       | US 2000-177836P  | 20000125 (60) |
|                       | US 2000-178368P  | 20000127 (60) |
|                       | US 2000-210292P  | 20000608 (60) |
| DOCUMENT TYPE:        | Utility  |               |
| FILE SEGMENT:         | APPLICATION  |               |
| LEGAL REPRESENTATIVE: | Patrea L. Pabst, Arnall Golden & Gregory, LLP, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA, 30309-3450 |               |
| NUMBER OF CLAIMS:     | 23   |               |
| EXEMPLARY CLAIM:      | 1  |               |
| NUMBER OF DRAWINGS:   | 12 Drawing Page(s)   |               |
| LINE COUNT:           | 2377   |               |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for the production of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been determined. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit

the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogues including isosteres at the sites of the critical amino acid residues were developed and the substrate analogues, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (FIG. 1). The inhibition constant of OM99-2 is 1.6.times.10.sup.-9 M against recombinant pro-memapsin 2. Crystallography of memapsin 2 bound to this inhibitor was used to determine the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using commercially available software programs and techniques familiar to those in organic chemistry and enzymology, to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

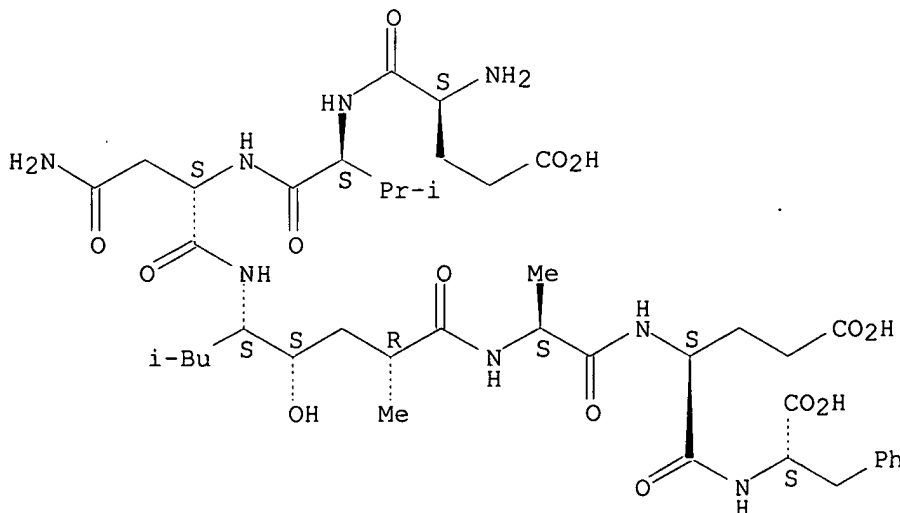
IT 314266-76-7DP, OM 99-2, complexes with memapsin 2

(catalytically active recombinant memapsin 2, 3D crystal structure based inhibitor design, synthesis, and screening, for Alzheimer's disease treatment)

RN 314266-76-7 USPATFULL

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 9 OF 9 .USPATFULL

ACCESSION NUMBER: 2002:92777 USPATFULL

TITLE: Catalytically active recombinant memapsin and methods of use thereof

INVENTOR(S): Tang, Jordan J. N., Edmond, OK, UNITED STATES

Lin, Xinli, Edmond, OK, UNITED STATES

Koelsch, Gerald, Oklahoma City, OK, UNITED STATES



Hong, Lin, Oklahoma City, OK, UNITED STATES

|                       | NUMBER   | KIND | DATE         |
|-----------------------|--|------|--------------|
| PATENT INFORMATION:   | US 2002049303  | A1   | 20020425     |
| APPLICATION INFO.:    | US 2001-796264   | A1   | 20010228 (9) |
| RELATED APPLN. INFO.: | Division of Ser. No. US 2000-604608, filed on 27 Jun 2000, PENDING |      |              |

|                       | NUMBER  | DATE          |
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| PRIORITY INFORMATION: | US 1999-141363P   | 19990628 (60) |
|                       | US 1999-168060P   | 19991130 (60) |
|                       | US 2000-177836P   | 20000125 (60) |
|                       | US 2000-178368P   | 20000127 (60) |
| DOCUMENT TYPE:        | Utility   |               |
| FILE SEGMENT:         | APPLICATION   |               |
| LEGAL REPRESENTATIVE: | PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400 |               |
| NUMBER OF CLAIMS:     | 33  |               |
| EXEMPLARY CLAIM:      | 1   |               |
| NUMBER OF DRAWINGS:   | 12 Drawing Page(s)  |               |
| LINE COUNT:           | 2441  |               |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for the production of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been determined. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the critical amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (FIG. 1). The inhibition constant of OM99-2 is 1.6.times.10.sup.-9 M against recombinant pro-memapsin 2. Crystallography of memapsin 2 bound to this inhibitor was used to determine the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using commercially available software programs and techniques familiar to those in organic chemistry and enzymology, to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of **Alzheimer's** disease.

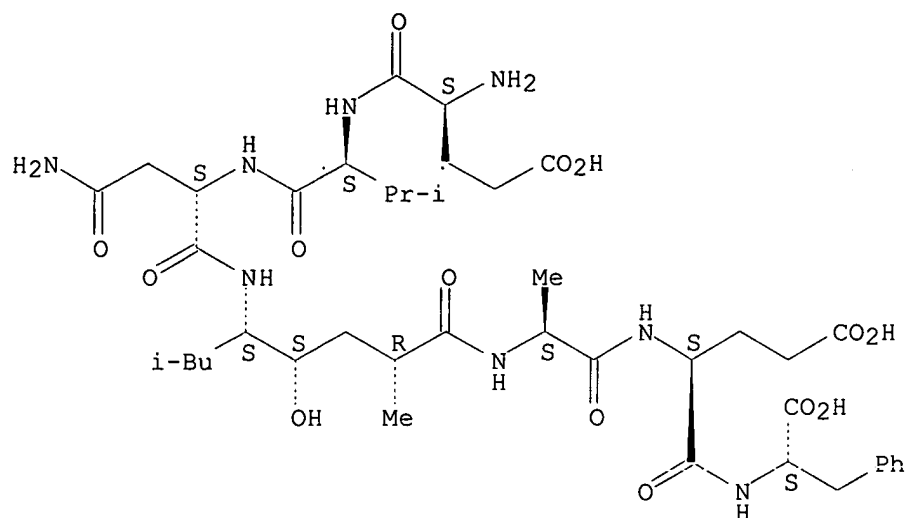
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 314266-76-7DP, OM 99-2, complexes with memapsin 2  
(catalytically active recombinant memapsin 2, 3D crystal structure based inhibitor design, synthesis, and screening, for Alzheimer's disease treatment)

RN 314266-76-7 USPATFULL

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



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STRUCTURE FILE UPDATES: 31 MAR 2003 HIGHEST RN 501072-24-8

DICTIONARY FILE UPDATES: 31 MAR 2003 HIGHEST RN 501072-24-8

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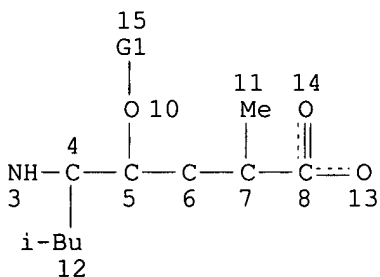
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Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

L28

STR



*Note: This structure was searched to cover the compounds of 37e and 40a, whose structures were not included in the CAS reference of the inventors' work.*

*Please note: Structures 1-4 retrieved in the full file search do not match the structures of 37e and 40a. So these compounds are not present in CAS + could not be searched as products or reactants*

VAR G1=H/SI

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CONNECT IS E1 RC AT 13

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE

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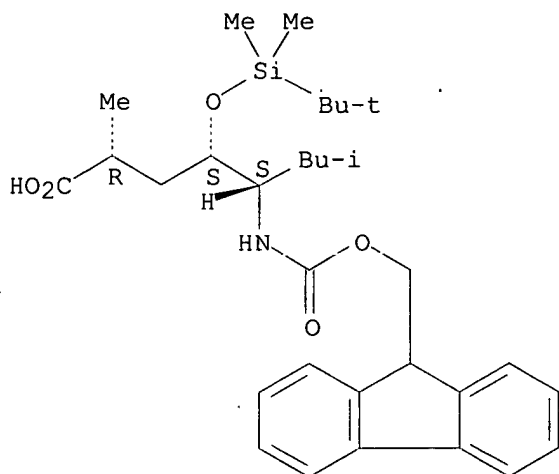
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Absolute stereochemistry.

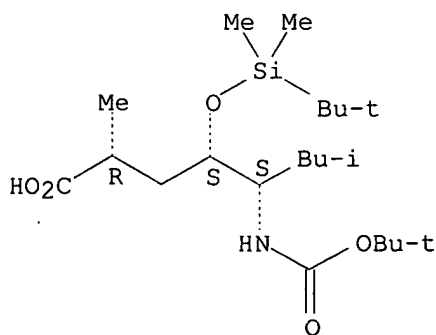


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

3 REFERENCES IN FILE CA (1962 TO DATE)  
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L30 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2003 ACS  
RN 271601-65-1 REGISTRY  
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LC STN Files: CA, CAPLUS

Absolute stereochemistry.

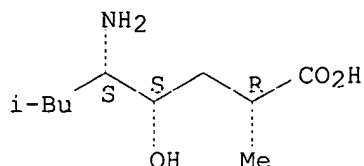


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

4 REFERENCES IN FILE CA (1962 TO DATE)  
4 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L30 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2003 ACS  
RN 91464-94-7 REGISTRY  
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LC STN Files: CA, CAPLUS

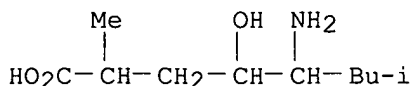
Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

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1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L30 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2003 ACS  
RN 89028-17-1 REGISTRY  
CN Octanoic acid, 5-amino-4-hydroxy-2,7-dimethyl- (9CI) (CA INDEX NAME)  
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LC STN Files: CA, CAPLUS



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FILE LAST UPDATED: 31 Mar 2003 (20030331/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/BI)

L16 2 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C16H27NO5/ME

L31 3 SEA FILE=CAPLUS ABB=ON PLU=ON L16/P

*Note: L31 = compound in claim 37a as a product*

=> d ibib abs hitstr l31 1-3

L31 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2001:12489 CAPLUS  
DOCUMENT NUMBER: 134:80832  
TITLE: Inhibitors of memapsin 2 and use thereof  
INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.  
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois  
SOURCE: PCT Int. Appl., 86 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

| PATENT NO.    | KIND | DATE     | APPLICATION NO. | DATE     |
|---------------|------|----------|-----------------|----------|
| WO 2001000665 | A2   | 20010104 | WO 2000-US17742 | 20000627 |
| WO 2001000665 | A3   | 20010927 |                 |          |
| WO 2001000665 | C2   | 20020725 |                 |          |

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,  
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1194449 A2 20020410 EP 2000-943236 20000627

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO

JP 2003506322 T2 20030218 JP 2001-507071 20000627

US 2002049303 A1 20020425 US 2001-796264 20010228

US 2002164760 A1 20021107 US 2001-795903 20010228

US 2002115600 A1 20020822 US 2001-845226 20010430

PRIORITY APPLN. INFO.:

US 1999-141363P P 19990628

US 1999-168060P P 19991130

US 2000-177836P P 20000125

US 2000-178368P P 20000127

US 2000-210292P P 20000608

US 2000-603713 A3 20000627

US 2000-604608 A3 20000627

WO 2000-US17742 W 20000627

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is  $1.6 \times 10^{-9}$  M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

IT 105018-82-4P 105018-89-1P

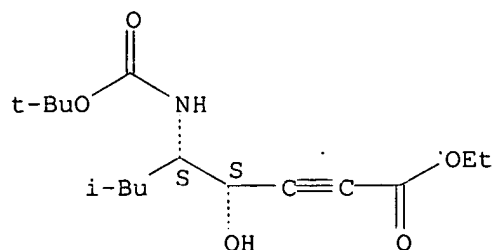
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(inhibitors of memapsin 2 and use thereof)

RN 105018-82-4 CAPLUS

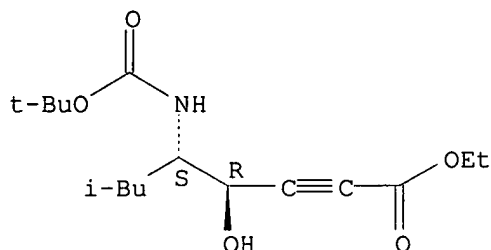
CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 105018-89-1 CAPLUS  
 CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

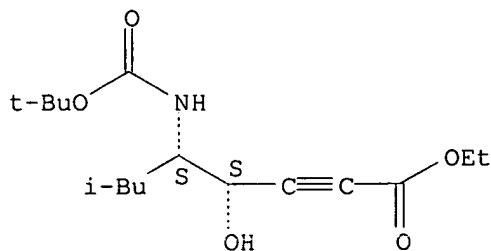


L31 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:188678 CAPLUS  
 DOCUMENT NUMBER: 133:12663  
 TITLE: Design of potent inhibitors for human brain memapsin 2 (.beta.-secretase)  
 AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch, Gerald; Lin, Xinli; Ermolieff, Jacques; Tang, Jordan  
 CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA  
 SOURCE: Journal of the American Chemical Society (2000), 122(14), 3522-3523  
 CODEN: JACSAT; ISSN: 0002-7863  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Two highly potent inhibitors of human memapsin 2 were designed and synthesized from current available specificity information. The inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant human memapsin 2 prepd. from E. coli expression.  
 IT 105018-82-4P 105018-89-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (prepn. and activity of potent inhibitors for human brain memapsin 2 (.beta.-secretase))

RN 105018-82-4 CAPLUS  
 CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

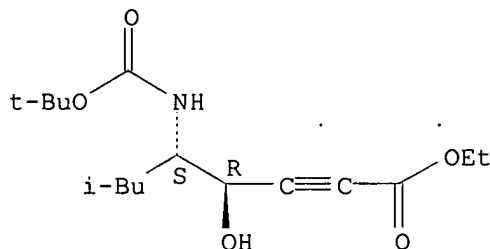


RN 105018-89-1 CAPLUS



CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1986:627255 CAPLUS

DOCUMENT NUMBER: 105:227255

TITLE: A short, stereoselective synthesis of the lactone precursor to 2R,4S,5S hydroxyethylene dipeptide isosteres

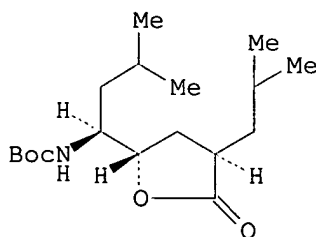
AUTHOR(S): Fray, Andrew H.; Kaye, Robert L.; Kleinman, Edward F.  
CORPORATE SOURCE: Dep. Med. Chem., Pfizer, Inc., Groton, CT, 06340, USA  
SOURCE: Journal of Organic Chemistry (1986), 51(25), 4828-33  
CODEN: JOCEAH; ISSN: 0022-3263

DOCUMENT TYPE: Journal

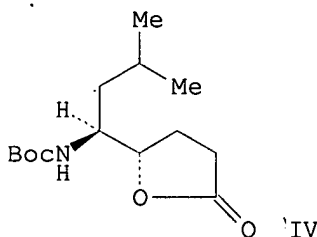
LANGUAGE: English

OTHER SOURCE(S): CASREACT 105:227255

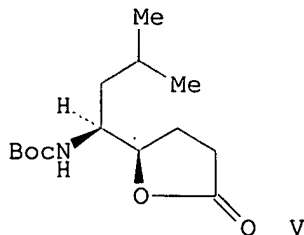
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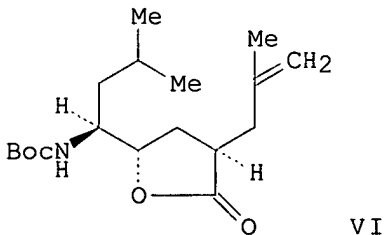
I



IV



V



VI

AB Lactone I (Boc = Me<sub>3</sub>CO<sub>2</sub>C), a precursor to the 2R,4S,5S hydroxyethylene dipeptide isostere unit, was synthesized stereoselectively in 4 steps from N-Boc-L-leucinal (II) in 13% overall yield. Addn. of LiC.tplbond.CCO<sub>2</sub>Et to II gave Me<sub>2</sub>CHCH<sub>2</sub>CH(NHBoc)CH(OH)C.tplbond.CCO<sub>2</sub>Et (III) as a mixt. of the (4S,5S)- and (4R,5S)-diastereomers. Redn. of the acetylenic function of

III and subsequent lactonization gave a readily separable 4.5:1 mixt. of acetones IV and V. Direct alkylation of IV with methallyl bromide and lithium hexamethyldisilazide as base yielded lactone VI, which was catalytically reduced to I. The structure of VI was confirmed by x-ray anal. Peptides contg. hydroxyethylene dipeptide isosteres with the above chirality are potent inhibitors of aspartyl proteases.

IT 105018-82-4P 105018-89-1P

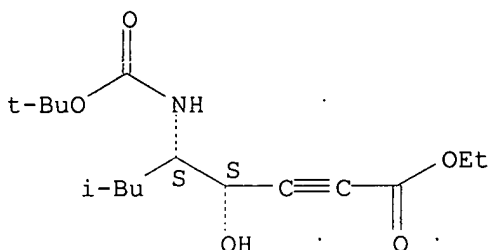
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. and hydrogenation-lactonization of)

RN 105018-82-4 CAPLUS

CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

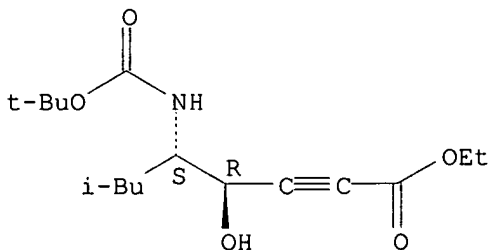
Absolute stereochemistry.



RN 105018-89-1 CAPLUS

CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d que 140

L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/BI)

BI)  
 L16 2 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C16H27NO5/MF  
 L17 2 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C14H25NO4/MF  
 L40 3 SEA FILE=CAPLUS ABB=ON PLU=ON L17/P AND L16 (L) (RCT OR  
 RACT)/RL

*Note: 140 = compound of claim 37c as a product*

=> d ibib abs hitstr 140 1-3

L40 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:12489 CAPLUS  
 DOCUMENT NUMBER: 134:80832  
 TITLE: Inhibitors of memapsin 2 and use thereof  
 INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.  
 PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board  
 of Trustees of the University of Illinois  
 SOURCE: PCT Int. Appl., 86 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

| PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE     |
|--|------|----------|-----------------|----------|
| WO 2001000665  | A2   | 20010104 | WO 2000-US17742 | 20000627 |
| WO 2001000665  | A3   | 20010927 |                 |          |
| WO 2001000665  | C2   | 20020725 |                 |          |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,<br>CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,<br>IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,<br>MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,<br>SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ,<br>BY, KG, KZ, MD, RU, TJ, TM<br>RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,<br>DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,<br>CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG<br>EP 1194449 A2 20020410 EP 2000-943236 20000627<br>R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,<br>IE, SI, LT, LV, FI, RO<br>JP 2003506322 T2 20030218 JP 2001-507071 20000627<br>US 2002049303 A1 20020425 US 2001-796264 20010228<br>US 2002164760 A1 20021107 US 2001-795903 20010228<br>US 2002115600 A1 20020822 US 2001-845226 20010430<br>PRIORITY APPLN. INFO.:<br>US 1999-141363P P 19990628<br>US 1999-168060P P 19991130<br>US 2000-177836P P 20000125<br>US 2000-178368P P 20000127<br>US 2000-210292P P 20000608<br>US 2000-603713 A3 20000627<br>US 2000-604608 A3 20000627<br>WO 2000-US17742 W 20000627 |      |          |                 |          |

AB Methods for the prodn. of purified, catalytically active, recombinant  
 memapsin 2 have been developed. The substrate and subsite specificity of  
 the catalytically active enzyme have been detd. The substrate and subsite  
 specificity information was used to design substrate analogs of the  
 natural memapsin 2 substrate that can inhibit the function of memapsin 2.  
 The substrate analogs are based on peptide sequences, shown to be related  
 to the natural peptide substrates for memapsin 2. The substrate analogs  
 contain at least one analog of an amide bond which is not capable of being  
 cleaved by memapsin 2. Processes for the synthesis of two substrate

analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is  $1.6 \times 10^{-9}$  M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

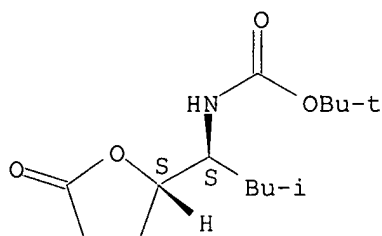
IT 105018-81-3P 105018-82-4P 105018-83-5P  
105018-89-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(inhibitors of memapsin 2 and use thereof)

RN 105018-81-3 CAPLUS

CN Carbamic acid, [(1S)-3-methyl-1-[(2S)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

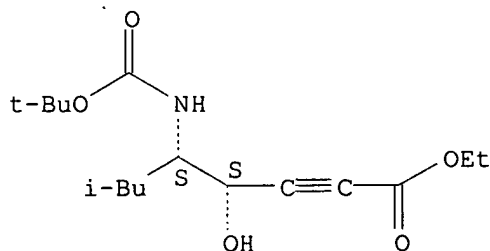
Absolute stereochemistry.



RN 105018-82-4 CAPLUS

CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

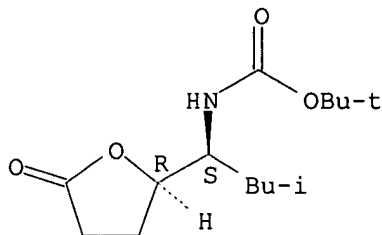
Absolute stereochemistry.



RN 105018-83-5 CAPLUS

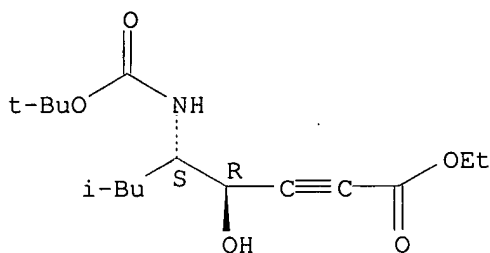
CN Carbamic acid, [(1S)-3-methyl-1-[(2R)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



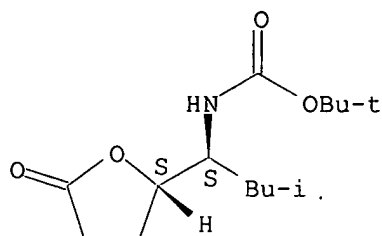
RN 105018-89-1 CAPLUS  
 CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L40 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:188678 CAPLUS  
 DOCUMENT NUMBER: 133:12663  
 TITLE: Design of potent inhibitors for human brain memapsin 2  
 (.beta.-secretase)  
 AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch,  
 Gerald; Lin, Xinli; Ermolieff, Jacques; Tang, Jordan  
 CORPORATE SOURCE: Department of Chemistry, University of Illinois at  
 Chicago, Chicago, IL, USA  
 SOURCE: Journal of the American Chemical Society (2000),  
 122(14), 3522-3523  
 CODEN: JACSAT; ISSN: 0002-7863  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Two highly potent inhibitors of human memapsin 2 were designed and  
 synthesized from current available specificity information. The  
 inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant  
 human memapsin 2 prep. from E. coli expression.  
 IT 105018-81-3P 105018-82-4P 105018-83-5P  
 105018-89-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP  
 (Preparation); RACT (Reactant or reagent)  
 (prepn. and activity of potent inhibitors for human brain memapsin 2  
 (.beta.-secretase))  
 RN 105018-81-3 CAPLUS  
 CN Carbamic acid, [(1S)-3-methyl-1-[(2S)-tetrahydro-5-oxo-2-furanyl]butyl]-,  
 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

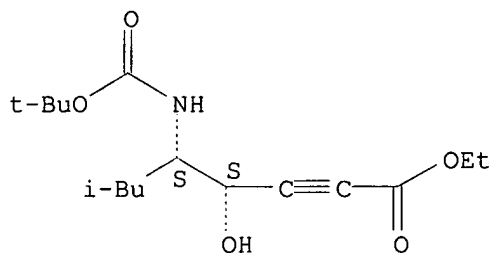
Absolute stereochemistry.



RN 105018-82-4 CAPLUS

CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

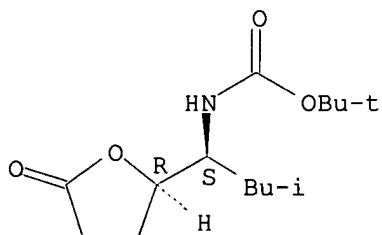
Absolute stereochemistry.



RN 105018-83-5 CAPLUS

CN Carbamic acid, [(1S)-3-methyl-1-[(2R)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

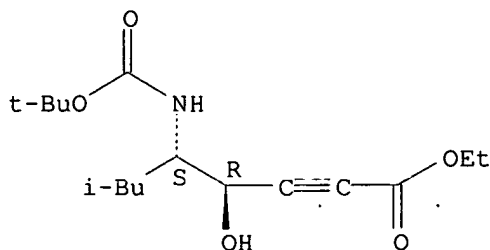
Absolute stereochemistry.



RN 105018-89-1 CAPLUS

CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L40 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1986:627255 CAPLUS

DOCUMENT NUMBER: 105:227255

TITLE: A short, stereoselective synthesis of the lactone precursor to 2R,4S,5S hydroxyethylene dipeptide isosteres

AUTHOR(S): Fray, Andrew H.; Kaye, Robert L.; Kleinman, Edward F.

CORPORATE SOURCE: Dep. Med. Chem., Pfizer, Inc., Groton, CT, 06340, USA

SOURCE: Journal of Organic Chemistry (1986), 51(25), 4828-33

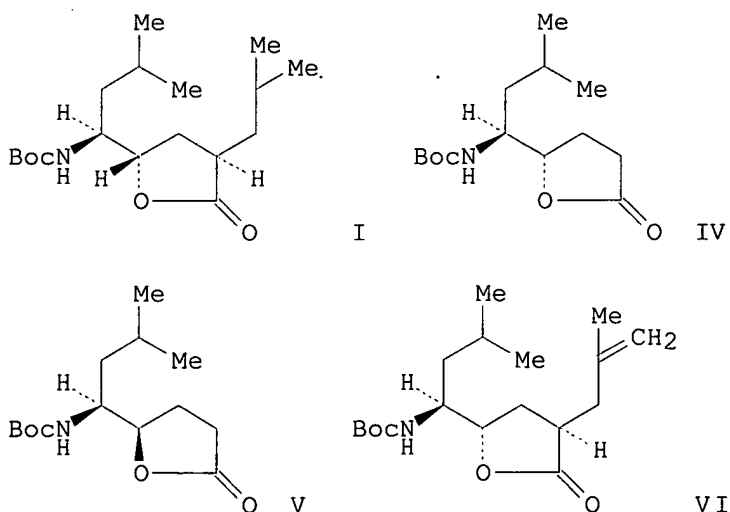
CODEN: JOCEAH; ISSN: 0022-3263

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 105:227255

GI



AB Lactone I (Boc = Me<sub>3</sub>CO<sub>2</sub>C), a precursor to the 2R,4S,5S hydroxyethylene dipeptide isostere unit, was synthesized stereoselectively in 4 steps from N-Boc-L-leucinal (II) in 13% overall yield. Addn. of LiC.tplbond.CCO<sub>2</sub>Et to II gave Me<sub>2</sub>CHCH<sub>2</sub>CH(NHBoc)CH(OH)C.tplbond.CCO<sub>2</sub>Et (III) as a mixt. of the (4S,5S)- and (4R,5S)-diastereomers. Redn. of the acetylenic function of III and subsequent lactonization gave a readily separable 4.5:1 mixt. of acetones IV and V. Direct alkylation of IV with methallyl bromide and lithium hexamethyldisilazide as base yielded lactone VI, which was catalytically reduced to I. The structure of VI was confirmed by x-ray anal. Peptides contg. hydroxyethylene dipeptide isosteres with the above chirality are potent inhibitors of aspartyl proteases.

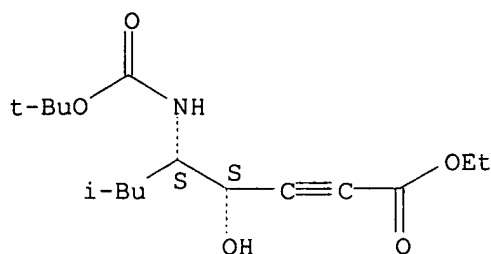
IT 105018-82-4P 105018-89-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (prepn. and hydrogenation-lactonization of)

RN 105018-82-4 CAPLUS

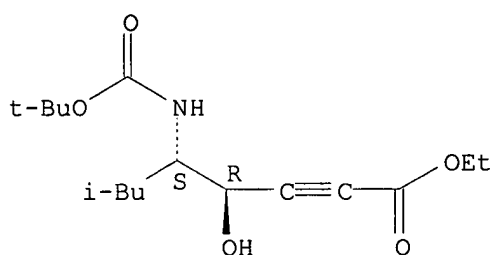
CN 2-Octynoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



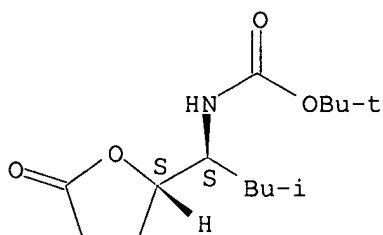
RN 105018-89-1 CAPLUS  
 CN 2-Octynoic acid, 5-[[[1,1-dimethylethoxy]carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 105018-81-3P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (prepn. and stereoselective alkylation of, with methallyl bromide)  
 RN 105018-81-3 CAPLUS  
 CN Carbamic acid, [(1S)-3-methyl-1-[(2S)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

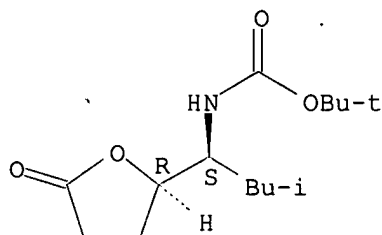
Absolute stereochemistry.



IT 105018-83-5P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of)  
 RN 105018-83-5 CAPLUS  
 CN Carbamic acid, [(1S)-3-methyl-1-[(2R)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.





=&gt; d que 141

L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/BI)

L17 2 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C14H25NO4/MF

L18 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C15H27NO4/MF

L41 4 SEA FILE=CAPLUS ABB=ON PLU=ON L18/P AND L17 (L) (RCT OR RACT)/RL

*Note: L41 = compound of 37d as a product*

=&gt; d ibib abs 141 1-4

L41 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:521789 CAPLUS

DOCUMENT NUMBER: 137:90187

TITLE: Inhibitors of memapsin 2 and their use in Alzheimer's disease treatment

INVENTOR(S): Tang, Jordan J. N.; Koelsch, Gerald; Ghosh, Arun K.

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois

SOURCE: PCT Int. Appl., 74 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE     |
|--|------|----------|-----------------|----------|
| WO 2002053594  | A2   | 20020711 | WO 2001-US50826 | 20011228 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, |      |          |                 |          |

UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,  
TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,  
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2000-258705P P 20001228

US 2001-275756P P 20010314

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. by a method which detcs. the initial hydrolysis rate of the substrate by using MALDI-TOF/MS. Alternatively, the subsite specificity of memapsin can be detd. by probing a library of inhibitors with memapsin 2 and subsequently detecting the bound memapsin 2 with an antibody raised to memapsin 2 and an alk. phosphatase conjugated secondary antibody. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the more than seventy substrate analogs were synthesized, among which MMI-005, MMI-012, MMI-017, MMI-018, MMI-025, MMI-026, MMI-037, MMI-039, MMI-040, MMI-066, MMI-070, and MMI-071 have inhibition consts. in the range of  $1.4\text{--}61.4 \times 10^9$  M against recombinant pro-memapsin 2. These inhibitors are useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

L41 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:558376 CAPLUS

DOCUMENT NUMBER: 135:282682

TITLE: Structure-based design: potent inhibitors of human brain memapsin 2 (.beta.-secretase)

AUTHOR(S): Ghosh, Arun K.; Bilcer, Geoffrey; Harwood, Cynthia; Kawahama, Reiko; Shin, Dongwoo; Hussain, Khaja Azhar; Hong, Lin; Loy, Jeffrey A.; Nguyen, Chan; Koelsch, Gerald; Ermoloeff, Jacques; Tang, Jordan

CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, 60607, USA

SOURCE: Journal of Medicinal Chemistry (2001), 44(18), 2865-2868

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Memapsin 2 (.beta.-secretase) is one of two proteases that cleave the .beta.-amyloid precursor protein (APP) to produce the 40-42 residue amyloid-.beta. peptide (A.beta.) in the human brain, a key event in the progression of Alzheimer's disease. On the basis of the X-ray crystal structure of our lead inhibitor (2, OM99-2 with eight residues) bound to memapsin, we have reduced the mol. wt. and designed potent memapsin inhibitors. Structure-based design and preliminary structure-activity studies have been presented.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:12489 CAPLUS

DOCUMENT NUMBER: 134:80832

TITLE: Inhibitors of memapsin 2 and use thereof

INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.  
 PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board  
 of Trustees of the University of Illinois  
 SOURCE: PCT Int. Appl., 86 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|---|------|----------|-----------------|----------|
| WO 2001000665   | A2   | 20010104 | WO 2000-US17742 | 20000627 |
| WO 2001000665   | A3   | 20010927 |                 |          |
| WO 2001000665   | C2   | 20020725 |                 |          |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,<br>CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,<br>IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,<br>MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,<br>SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ,<br>BY, KG, KZ, MD, RU, TJ, TM<br>RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,<br>DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,<br>CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  |      |          |                 |          |
| EP 1194449  | A2   | 20020410 | EP 2000-943236  | 20000627 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,<br>IE, SI, LT, LV, FI, RO  |      |          |                 |          |
| JP 2003506322   | T2   | 20030218 | JP 2001-507071  | 20000627 |
| US 2002049303   | A1   | 20020425 | US 2001-796264  | 20010228 |
| US 2002164760   | A1   | 20021107 | US 2001-795903  | 20010228 |
| US 2002115600   | A1   | 20020822 | US 2001-845226  | 20010430 |
| PRIORITY APPLN. INFO.:<br>US 1999-141363P P 19990628<br>US 1999-168060P P 19991130<br>US 2000-177836P P 20000125<br>US 2000-178368P P 20000127<br>US 2000-210292P P 20000608<br>US 2000-603713 A3 20000627 ✓<br>US 2000-604608 A3 20000627<br>WO 2000-US17742 W 20000627  |      |          |                 |          |
| AB Methods for the prodn. of purified, catalytically active, recombinant<br>memapsin 2 have been developed. The substrate and subsite specificity of<br>the catalytically active enzyme have been detd. The substrate and subsite<br>specificity information was used to design substrate analogs of the<br>natural memapsin 2 substrate that can inhibit the function of memapsin 2.<br>The substrate analogs are based on peptide sequences, shown to be related<br>to the natural peptide substrates for memapsin 2. The substrate analogs<br>contain at least one analog of an amide bond which is not capable of being<br>cleaved by memapsin 2. Processes for the synthesis of two substrate<br>analogs including isosteres at the sites of the crit. amino acid residues<br>were developed and the substrate analogs, OMR99-1 and OM99-2, were<br>synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-<br>Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a<br>transition-state isostere hydroxyethylene group (Figure 1). The<br>inhibition const. of OM99-2 is $1.6 \times 10^{-9}$ M against recombinant<br>pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was<br>used to det. the three dimensional structure of the protein, as well as<br>the importance of the various residues in binding. This information can<br>be used by those skilled in the art to design new inhibitors, using com.<br>available software programs and techniques familiar to those in org. chem.<br>and enzymol., to design new inhibitors to memapsin 2, useful in<br>diagnostics and for the treatment and/or prevention of Alzheimer's |      |          |                 |          |

disease.

L41 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2000:188678 CAPLUS  
 DOCUMENT NUMBER: 133:12663  
 TITLE: Design of potent inhibitors for human brain memapsin 2  
 (.beta.-secretase)  
 AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch,  
 Gerald; Lin, Xinli; Ermolieff, Jacques; Tang, Jordan  
 CORPORATE SOURCE: Department of Chemistry, University of Illinois at  
 Chicago, Chicago, IL, USA  
 SOURCE: Journal of the American Chemical Society (2000),  
 122(14), 3522-3523  
 CODEN: JACSAT; ISSN: 0002-7863  
 PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Two highly potent inhibitors of human memapsin 2 were designed and  
 synthesized from current available specificity information. The  
 inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant  
 human memapsin 2 prepd. from E. coli expression.  
 REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=&gt; d que 144

L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-  
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 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6  
 /BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR  
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 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI  
 OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/  
 BI)  
 L20 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C13H26N2O4/MF  
 L21 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C11H21NO4/MF  
 L44 2 SEA FILE=CAPLUS ABB=ON PLU=ON L21/P AND L20 (L) (RCT OR  
 RACT)/RL

*note: L44 = compounds of 38b as a product combined with 38a as a  
 reactant*

=&gt; bib abs 144 1-2

L44 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:521789 CAPLUS  
 DOCUMENT NUMBER: 137:90187  
 TITLE: Inhibitors of memapsin 2 and their use in Alzheimer's  
 disease treatment  
 INVENTOR(S): Tang, Jordan J. N.; Koelsch, Gerald; Ghosh, Arun K.  
 PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board  
 of Trustees of the University of Illinois  
 SOURCE: PCT Int. Appl., 74 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

## PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|---|------|----------|-----------------|----------|
| WO 2002053594   | A2   | 20020711 | WO 2001-US50826 | 20011228 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |      |          |                 |          |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  |      |          |                 |          |

PRIORITY APPLN. INFO.: US 2000-258705P P 20001228

US 2001-275756P P 20010314

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. by a method which detd. the initial hydrolysis rate of the substrate by using MALDI-TOF/MS. Alternatively, the subsite specificity of memapsin can be detd. by probing a library of inhibitors with memapsin 2 and subsequently detecting the bound memapsin 2 with an antibody raised to memapsin 2 and an alk. phosphatase conjugated secondary antibody. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the more than seventy substrate analogs were synthesized, among which MMI-005, MMI-012, MMI-017, MMI-018, MMI-025, MMI-026, MMI-037, MMI-039, MMI-040, MMI-066, MMI-070, and MMI-071 have inhibition consts. in the range of 1:4-61.4 x 10<sup>9</sup> M against recombinant pro-memapsin 2. These inhibitors are useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

L44 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:12489 CAPLUS

DOCUMENT NUMBER: 134:80832

TITLE: Inhibitors of memapsin 2 and use thereof

INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois

SOURCE: PCT Int. Appl., 86 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

## PATENT INFORMATION:

| PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE     |
|--|------|----------|-----------------|----------|
| WO 2001000665  | A2   | 20010104 | WO 2000-US17742 | 20000627 |
| WO 2001000665  | A3   | 20010927 |                 |          |
| WO 2001000665  | C2   | 20020725 |                 |          |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, |      |          |                 |          |

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
 MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,  
 SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ,  
 BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,  
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 EP 1194449 A2 20020410 EP 2000-943236 20000627  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO  
 JP 2003506322 T2 20030218 JP 2001-507071 20000627  
 US 2002049303 A1 20020425 US 2001-796264 20010228  
 US 2002164760 A1 20021107 US 2001-795903 20010228  
 US 2002115600 A1 20020822 US 2001-845226 20010430  
 PRIORITY APPLN. INFO.: US 1999-141363P P 19990628  
 US 1999-168060P P 19991130  
 US 2000-177836P P 20000125  
 US 2000-178368P P 20000127  
 US 2000-210292P P 20000608  
 US 2000-603713 A3 20000627  
 US 2000-604608 A3 20000627  
 WO 2000-US17742 W 20000627  
 AB Methods for the prodn. of purified, catalytically active, recombinant  
 memapsin 2 have been developed. The substrate and subsite specificity of  
 the catalytically active enzyme have been detd. The substrate and subsite  
 specificity information was used to design substrate analogs of the  
 natural memapsin 2 substrate that can inhibit the function of memapsin 2.  
 The substrate analogs are based on peptide sequences, shown to be related  
 to the natural peptide substrates for memapsin 2. The substrate analogs  
 contain at least one analog of an amide bond which is not capable of being  
 cleaved by memapsin 2. Processes for the synthesis of two substrate  
 analogs including isosteres at the sites of the crit. amino acid residues  
 were developed and the substrate analogs, OMR99-1 and OM99-2, were  
 synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-  
 Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a  
 transition-state isostere hydroxyethylene group (Figure 1). The  
 inhibition const. of OM99-2 is  $1.6 \times 10^{-9}$  M against recombinant  
 pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was  
 used to det. the three dimensional structure of the protein, as well as  
 the importance of the various residues in binding. This information can  
 be used by those skilled in the art to design new inhibitors, using com.  
 available software programs and techniques familiar to those in org. chem.  
 and enzymol., to design new inhibitors to memapsin 2, useful in  
 diagnostics and for the treatment and/or prevention of Alzheimer's  
 disease.

=> d hitstr 144 1-4

L44 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS

IT 13139-15-6P 87694-50-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP

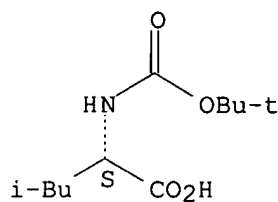
(Preparation); RACT (Reactant or reagent)

(inhibitors of memapsin 2 and their use in Alzheimer's disease  
 treatment)

RN 13139-15-6 CAPLUS

CN L-Leucine, N-[(1,1-dimethylethoxy)carbonyl]- (9CI) (CA INDEX NAME)

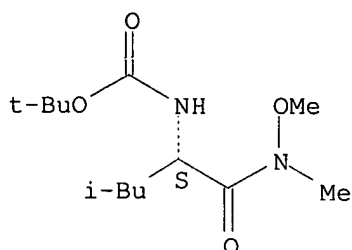
Absolute stereochemistry. Rotation (-).



RN 87694-50-6 CAPLUS

CN Carbamic acid, [(1S)-1-[(methoxymethylamino)carbonyl]-3-methylbutyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L44 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS

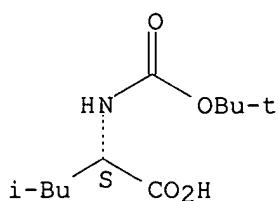
IT 13139-15-6P 87694-50-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (inhibitors of memapsin 2 and use thereof)

RN 13139-15-6 CAPLUS

CN L-Leucine, N-[(1,1-dimethylethoxy)carbonyl]- (9CI) (CA INDEX NAME)

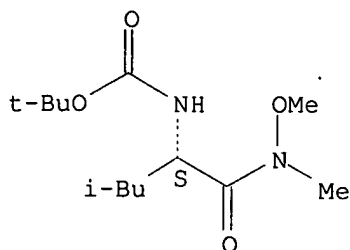
Absolute stereochemistry. Rotation (-).



RN 87694-50-6 CAPLUS

CN Carbamic acid, [(1S)-1-[(methoxymethylamino)carbonyl]-3-methylbutyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



=&gt; d que 136

L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/BI).

L22

1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C21H43NO5SI/MF

L36

4 SEA FILE=CAPLUS ABB=ON PLU=ON L22/P

*Note: L36= compounds of claim 39 as a product*

=&gt; d ibib abs hitstr 136 1-4

L36 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:521789 CAPLUS

DOCUMENT NUMBER: 137:90187

TITLE: Inhibitors of memapsin 2 and their use in Alzheimer's disease treatment

INVENTOR(S): Tang, Jordan J. N.; Koelsch, Gerald; Ghosh, Arun K.

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois

SOURCE: PCT Int. Appl., 74 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|---|------|----------|-----------------|----------|
| WO 2002053594   | A2   | 20020711 | WO 2001-US50826 | 20011228 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |      |          |                 |          |



RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,  
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-258705P P 20001228  
US 2001-275756P P 20010314

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. by a method which detd. the initial hydrolysis rate of the substrate by using MALDI-TOF/MS. Alternatively, the subsite specificity of memapsin can be detd. by probing a library of inhibitors with memapsin 2 and subsequently detecting the bound memapsin 2 with an antibody raised to memapsin 2 and an alk. phosphatase conjugated secondary antibody. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the more than seventy substrate analogs were synthesized, among which MMI-005, MMI-012, MMI-017, MMI-018, MMI-025, MMI-026, MMI-037, MMI-039, MMI-040, MMI-066, MMI-070, and MMI-071 have inhibition consts. in the range of  $1.4\text{--}61.4 \times 10^9$  M against recombinant pro-memapsin 2. These inhibitors are useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

IT 271601-65-1P

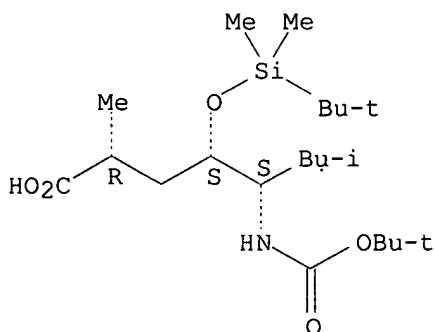
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(inhibitors of memapsin 2 and their use in Alzheimer's disease treatment)

RN 271601-65-1 CAPLUS

CN Octanoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L36 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:558376 CAPLUS

DOCUMENT NUMBER: 135:282682

TITLE: Structure-based design: potent inhibitors of human brain memapsin 2 (.beta.-secretase)

AUTHOR(S): Ghosh, Arun K.; Bilcer, Geoffrey; Harwood, Cynthia; Kawahama, Reiko; Shin, Dongwoo; Hussain, Khaja Azhar; Hong, Lin; Loy, Jeffrey A.; Nguyen, Chan; Koelsch,

CORPORATE SOURCE: Gerald; Ermoloeff, Jacques; Tang, Jordan  
Department of Chemistry, University of Illinois at  
Chicago, Chicago, IL, 60607, USA

SOURCE: Journal of Medicinal Chemistry (2001), 44(18),  
2865-2868  
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

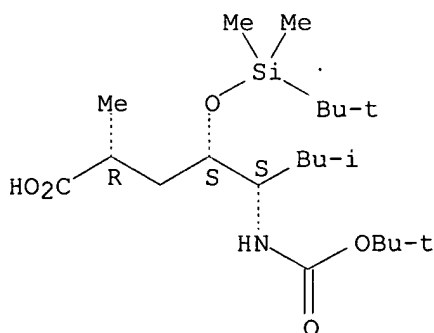
AB Memapsin 2 (.beta.-secretase) is one of two proteases that cleave the  
.beta.-amyloid precursor protein (APP) to produce the 40-42 residue  
amyloid-.beta. peptide (A.beta.) in the human brain, a key event in the  
progression of Alzheimer's disease. On the basis of the X-ray crystal  
structure of our lead inhibitor (2, OM99-2 with eight residues) bound to  
memapsin, we have reduced the mol. wt. and designed potent memapsin  
inhibitors. Structure-based design and preliminary structure-activity  
studies have been presented.

IT **271601-65-1P**  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP  
(Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL  
(Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or  
reagent)  
(structure-based design of memapsin 2 inhibitors for the treatment of  
Alzheimer's disease)

RN 271601-65-1 CAPLUS

CN Octanoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[[(1,1-  
dimethylethyl)dimethylsilyl]oxy]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:12489 CAPLUS

DOCUMENT NUMBER: 134:80832

TITLE: Inhibitors of memapsin 2 and use thereof

INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board  
of Trustees of the University of Illinois

SOURCE: PCT Int. Appl., 86 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent

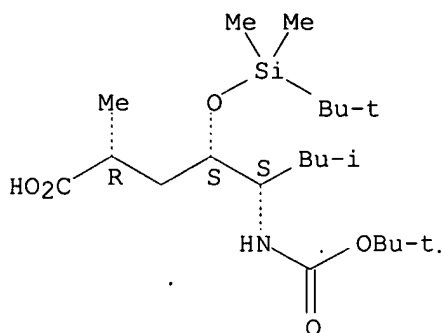
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO.  | KIND  | DATE     | APPLICATION NO. | DATE        |
|---|---|----------|-----------------|-------------|
| WO 2001000665   | A2  | 20010104 | WO 2000-US17742 | 20000627    |
| WO 2001000665   | A3  | 20010927 |                 |             |
| WO 2001000665   | C2  | 20020725 |                 |             |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM<br>RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG |   |          |                 |             |
| EP 1194449  | A2  | 20020410 | EP 2000-943236  | 20000627    |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO   |   |          |                 |             |
| JP 2003506322   | T2  | 20030218 | JP 2001-507071  | 20000627    |
| US 2002049303   | A1  | 20020425 | US 2001-796264  | 20010228    |
| US 2002164760   | A1  | 20021107 | US 2001-795903  | 20010228    |
| US 2002115600   | A1  | 20020822 | US 2001-845226  | 20010430    |
| PRIORITY APPLN. INFO.:  |   |          |                 |             |
|   |   |          | US 1999-141363P | P 19990628  |
|   |   |          | US 1999-168060P | P 19991130  |
|   |   |          | US 2000-177836P | P 20000125  |
|   |   |          | US 2000-178368P | P 20000127  |
|   |   |          | US 2000-210292P | P 20000608  |
|   |   |          | US 2000-603713  | A3 20000627 |
|   |   |          | US 2000-604608  | A3 20000627 |
|   |   |          | WO 2000-US17742 | W 20000627  |
| AB  | <p>Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is <math>1.6 \times 10^{-9}</math> M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.</p> |          |                 |             |
| IT  | <p><b>271601-65-1P</b><br/>           RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)<br/>           (inhibitors of memapsin 2 and use thereof)</p>   |          |                 |             |
| RN  | <p>271601-65-1 CAPLUS</p>   |          |                 |             |
| CN  | <p>Octanoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)</p>  |          |                 |             |

Absolute stereochemistry.



L36 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:188678 CAPLUS

DOCUMENT NUMBER: 133:12663

TITLE: Design of potent inhibitors for human brain memapsin 2  
(.beta.-secretase)

AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch,  
Gerald; Lin, Xinli; Ermolieff, Jacques; Tang, Jordan  
CORPORATE SOURCE: Department of Chemistry, University of Illinois at  
Chicago, Chicago, IL, USA

SOURCE: Journal of the American Chemical Society (2000),  
122(14), 3522-3523

CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two highly potent inhibitors of human memapsin 2 were designed and  
synthesized from current available specificity information. The  
inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant  
human memapsin 2 prep. from E. coli expression.

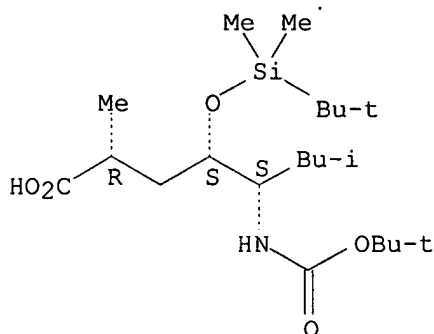
IT 271601-65-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(prepn. and activity of potent inhibitors for human brain memapsin 2  
(.beta.-secretase))

RN 271601-65-1 CAPLUS

CN Octanoic acid, 5-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[[(1,1-  
dimethylethyl)dimethylsilyl]oxy]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d que 137

L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/BI)

L24 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C31H45NO5SI/MF

3 SEA FILE=CAPLUS ABB=ON PLU=ON L24/P

*Note: L37 = compounds of claim 40 B as a product*

=> d bib abs hitstr 137 1-3

L37 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:521789 CAPLUS

DOCUMENT NUMBER: 137:90187

TITLE: Inhibitors of memapsin 2 and their use in Alzheimer's disease treatment

INVENTOR(S): Tang, Jordan J. N.; Koelsch, Gerald; Ghosh, Arun K.

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois

SOURCE: PCT Int. Appl., 74 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE     |
|--|------|----------|-----------------|----------|
| WO 2002053594  | A2   | 20020711 | WO 2001-US50826 | 20011228 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, |      |          |                 |          |

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,  
 PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,  
 UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,  
 TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,  
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2000-258705P P 20001228

US 2001-275756P P 20010314

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. by a method which detd. the initial hydrolysis rate of the substrate by using MALDI-TOF/MS. Alternatively, the subsite specificity of memapsin can be detd. by probing a library of inhibitors with memapsin 2 and subsequently detecting the bound memapsin 2 with an antibody raised to memapsin 2 and an alk. phosphatase conjugated secondary antibody. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the more than seventy substrate analogs were synthesized, among which MMI-005, MMI-012, MMI-017, MMI-018, MMI-025, MMI-026, MMI-037, MMI-039, MMI-040, MMI-066, MMI-070, and MMI-071 have inhibition consts. in the range of  $1.4\text{--}61.4 \times 10^9 \text{ M}$  against recombinant pro-memapsin 2. These inhibitors are useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

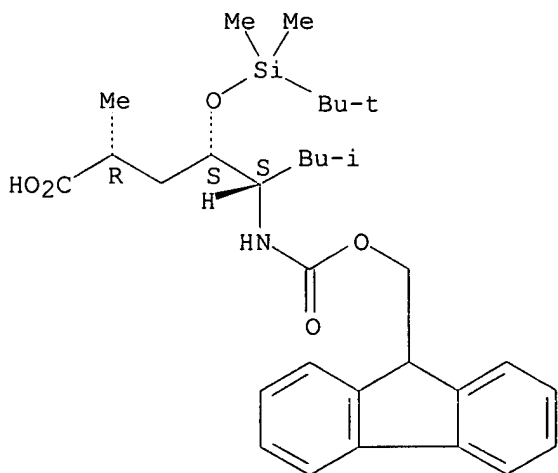
IT 271601-66-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (inhibitors of memapsin 2 and their use in Alzheimer's disease treatment)

RN 271601-66-2 CAPLUS

CN Octanoic acid, 4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L37 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:12489 CAPLUS  
 DOCUMENT NUMBER: 134:80832  
 TITLE: Inhibitors of memapsin 2 and use thereof  
 INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.  
 PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board  
 of Trustees of the University of Illinois  
 SOURCE: PCT Int. Appl., 86 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

| PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE     |
|--|------|----------|-----------------|----------|
| WO 2001000665  | A2   | 20010104 | WO 2000-US17742 | 20000627 |
| WO 2001000665  | A3   | 20010927 |                 |          |
| WO 2001000665  | C2   | 20020725 |                 |          |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  |      |          |                 |          |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG   |      |          |                 |          |
| EP 1194449   | A2   | 20020410 | EP 2000-943236  | 20000627 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO  |      |          |                 |          |
| JP 2003506322  | T2   | 20030218 | JP 2001-507071  | 20000627 |
| US 2002049303  | A1   | 20020425 | US 2001-796264  | 20010228 |
| US 2002164760  | A1   | 20021107 | US 2001-795903  | 20010228 |
| US 2002115600  | A1   | 20020822 | US 2001-845226  | 20010430 |
| PRIORITY APPLN. INFO.:   |      |          |                 |          |
| US 1999-141363P P 19990628   |      |          |                 |          |
| US 1999-168060P P 19991130   |      |          |                 |          |
| US 2000-177836P P 20000125   |      |          |                 |          |
| US 2000-178368P P 20000127   |      |          |                 |          |
| US 2000-210292P P 20000608   |      |          |                 |          |
| US 2000-603713 A3 20000627   |      |          |                 |          |
| US 2000-604608 A3 20000627   |      |          |                 |          |
| WO 2000-US17742 W 20000627   |      |          |                 |          |
| AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is $1.6 \times 10^{-9}$ M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was |      |          |                 |          |

used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

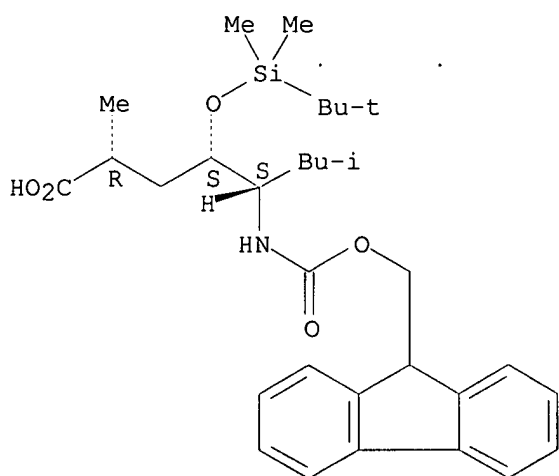
IT 271601-66-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(inhibitors of memapsin 2 and use thereof)

RN 271601-66-2 CAPLUS

CN Octanoic acid, 4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L37 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:188678 CAPLUS

DOCUMENT NUMBER: 133:12663

TITLE: Design of potent inhibitors for human brain memapsin 2 (.beta.-secretase)

AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch, Gerald; Lin, Xinli; Ermoloeff, Jacques; Tang, Jordan

CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA

SOURCE: Journal of the American Chemical Society (2000), 122(14), 3522-3523

CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two highly potent inhibitors of human memapsin 2 were designed and synthesized from current available specificity information. The inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant human memapsin 2 prepd. from E. coli expression.

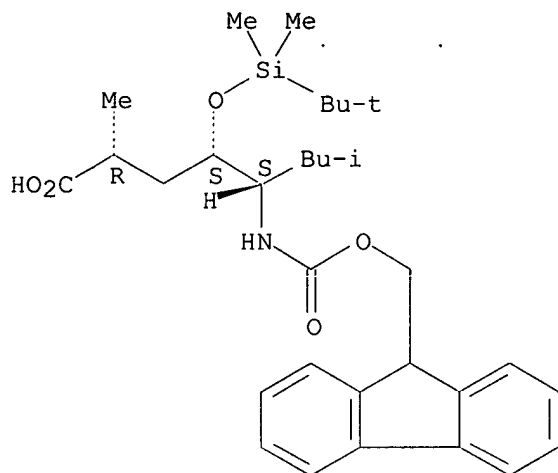
IT 271601-66-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(prepn. and activity of potent inhibitors for human brain memapsin 2



(.beta.-secretase))  
RN 271601-66-2 CAPLUS  
CN Octanoic acid, 4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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